Case Report

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Alagille syndrome and pregnancy

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Adam Morton[1] and Sailesh Kumar[2]

Abstract

Alagille syndrome is an autosomal dominant multisystem disorder with an estimated frequency of 1 in 30 000. Only a small number of pregnancy outcomes have been described in women with this condition. The report details the pregnancy outcomes of two women with Alagille syndrome. We also review the literature pertaining to this syndrome in pregnancy and demonstrate a significant risk of adverse pregnancy outcomes.

Keywords

Alagille syndrome, pregnancy, intrauterine growth restriction

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Introduction

Alagille syndrome (ALGS) is a complex multisystem condition caused by mutations in *JAG1* (98%) or *NOTCH2* (2%) genes. In approximately 60% of individuals with ALGS, the mutation occurs de novo, whilst the remainder are due to a likely autosomal dominant inheritance with an affected parent.[1] Characteristic features of ALGS include bile duct paucity (75–100%), cholestasis with pruritus (90–100%), cardiac malformations (85–98%), ocular disorders (55–95%), vertebral anomalies (25–85%), renal abnormalities (25–95%) including hypertension and renal artery stenosis, abnormal facies (70–98%), neurovascular abnormalities including intracranial bleeding and moyamoya syndrome (15%), immunodeficiency, recurrent infections and short stature (50–87%).[2] No genotype-phenotype correlations exist between the genetic mutations and the clinical manifestations of ALGS. Monozygotic twins with the *JAG1* mutation have been reported to display phenotypic discordance.[3]

ALGS may manifest significant intrafamilial variability for clinical manifestations. Although, liver disease is common, there is significant inconsistency in the course of liver disease without any factors being particularly predictive of disease progression. Approximately 15–47% of ALGS women develop unremitting cholestasis and progressive liver disease necessitating liver transplantation, whilst adults with *JAG1* or *NOTCH2* mutations without overt liver disease have also been described. As a result of the multisystem involvement, pregnancies in women with ALGS carry significant maternal and perinatal risks.

Case 1

A 29-year-old woman in her first pregnancy was transferred from another institution at 20 weeks' gestation because of hypertension, proteinuria and abnormal renal function. Her only relevant past history was of polycystic ovarian syndrome. She was not on any medication. The woman's adolescent half-sister had died following liver transplantation for ALGS. Physical examination revealed a body mass index of 34 kg/m^2, blood pressure of 150/100 mm Hg and an ejection systolic murmur. Her serum creatinine was 111 µmol/L (normal range 30–70 micromol/L), alanine transaminase 61 U/L (5–30U/L), aspartate transaminase 39 U/L (5–30U/L) and urine protein:creatinine ratio (PCR) was 179 mg/mmol (0–15mg/mmol). Abdominal ultrasound revealed normal hepato-biliary structures and bilateral renal cortical thinning and the absence of renal artery stenosis. Further investigations excluded phaeochromocytoma, primary aldosteronism, vasculitis and obstructive sleep apnoea. Maternal echocardiography demonstrated increased flow velocity through the right pulmonary artery branch suggestive of minor narrowing.

Labetalol 200 mg twice a day was commenced for persistent hypertension. At 33 weeks' gestation generalised pruritus developed. The serum bile acids were normal; however, she was commenced on ursodeoxycholic acid 1500 mg/day with resolution of itch. Progressive fetal growth restriction was noted on serial fetal growth scans. At 36 weeks' gestation she developed a significant rise in blood pressure, serum creatinine and urine PCR suggesting superimposed preeclampsia which prompted induction of labour. A live male infant, birthweight 2014 g, was delivered. Placental weight was 279 g (3rd–5th percentile for gestational age), with evidence of retroplacental haemorrhages and chronic villitis. The fetal/placental weight ratio was 7.2. Neonatal investigations revealed conjugated hyperbilirubinaemia, elevated hepatic transaminases and gamma glutamyl transferase, mild pulmonary valve stenosis and hypoplasia of the branch pulmonary arteries on echocardiography as well as multiple small echogenic medullary foci on renal ultrasound. Genetic testing of the infant revealed heterozygosity in the *JAG1* gene for a

[1]Obstetric Medicine and University of Queensland, Mater Health, Brisbane, Australia
[2]School of Medicine and Mater Research Institute, University of Queensland, South Brisbane, Australia

Corresponding author:
Adam Morton, Mater Health, Raymond Tce, South Brisbane, Queensland 4101, Australia.
Email: Adam.morton@mater.org.au

Table 1. Pregnancy outcomes in maternal Alagille syndrome.

Author	n	Fetus affected	Pregnancy outcomes
Albayram[9]	1	Yes	IUGR; preterm labour; delivery at 36 weeks; meconium stained liquor; 1535 g female; severe pulmonary stenosis; neonate died post-cardiac surgery
Witt[10]	4	?	#1 Miscarriage
		?	#2 Elective termination
		No	#3 Uncomplicated pregnancy delivery unaffected neonate at 39 weeks
		Yes	#4 Baby with mutation – no details of pregnancy given
Jung[11]	17	5	5 Fetuses with mutation – 4 pregnancies terminated No other details given
Rahmoune[12]	3		Mother had portal hypertension, hypersplenism, varices, type 1 diabetes mellitus
		No	#1 IUGR Maternal pulmonary oedema postpartum
		Yes	#2 HELLP syndrome
		Yes	#3 IUGR 1060 g female at 34 weeks
Antsalkis[13]	1	Yes	IUGR – terminated at 24 weeks' gestation, 640g female
Ferrarese[14]	1	No	Uncomplicated pregnancy – delivery at 38 weeks
Maissoneuve[15]	1	Yes	Mother liver/kidney transplant Uncomplicated pregnancy ; spontaneous labour 37 weeks; 2080 g female
Romero[16]	1	?	Maternal hepatosplenomegaly with thrombocytopenia Progressive hyperbilirubinaemia and pruritus in 3rd trimester IUGR; PPROM at 32 weeks; premature labour; birthweight 1190 g

variant designated c.1153del,p.His385Thrfs*27. The results for genetic testing on the mother are awaited.

Case 2

A 33-year-old woman in her first pregnancy presented for antenatal care at 14 weeks' gestation. ALGS with a *JAG1* mutation (heterozygosity for the c.2682 + 1G>A variant) had been diagnosed as an infant requiring pulmonary valvotomy and arterioplasty, and subsequent stenting of the left pulmonary artery. The woman manifested the triangular facies typical for ALGS with a broad forehead, deep-set eyes and a small pointed chin, as well as short stature. Liver and renal function tests were normal. Echocardiography demonstrated mild pulmonary stenosis and moderate pulmonary regurgitation. At 22 weeks' gestation she complained of a mild itch and although her serum bile acids were elevated she declined treatment. From 32 weeks' gestation a decrease in fetal growth velocity was seen on ultrasound. A healthy 2520 g male infant was delivered by cesarean section at 38 weeks' gestation after a failed instrumental delivery. Placental weight was 293 g, less than the 3rd percentile for gestational age, with multiple foci of intervillous haemorrhage. The fetal/placental weight ratio was 8.6. The neonate had no clinical features suggestive of ALGS and genetic testing was negative.

Discussion

Including the two cases detailed in this manuscript, there have been a total of only 11 successful pregnancies in women with ALGS described in the literature (Table 1). Of these, fetal growth restriction was present in seven pregnancies (64%), pre-eclampsia in two pregnancies (18%), and one case of postpartum maternal pulmonary oedema. Neonatal death following cardiac surgery occurred in one case.

Elmslie et al. reported relatively high miscarriage rates after 10 weeks' gestation in 6 of 22 women (27%) with ALGS.[4] There are however no published data regarding pregnancy outcomes in unaffected mothers where the fetus has a genetic mutation due to either paternal transmission or a de novo mutation.

Postulated causative factors for fetal growth restriction in women with ALGS include toxicity from bile acids, maternal vascular disease resulting in placental dysfunction and perturbations in placental growth factors.

Histopathology of placentae from women with intrahepatic cholestasis of pregnancy (ICP) complicated by fetal demise do not demonstrate features of chronic placental insufficiency. Placental histological findings from women with ICP include reduced intervillous spaces, crowded villi and an increased number of syncytial knots.[5,6] The absence of these histological changes despite the clinical evidence of fetal growth restriction in our two cases are consistent with maternal vasculopathy as the cause for the suboptimal fetal growth.

DNA-based pre-implantation and prenatal diagnosis of ALGS may be performed. Findings on prenatal ultrasound suggestive of ALGS include 'butterfly' hemivertebrae in the fetal lower thoracic spine, cardiac lesions, absent gallbladder, prominent chin and single umbilical artery.[7,8]

Important maternal management considerations for pregnancy include the severity of cardiac disease, particularly pulmonary hypertension, and the presence of cirrhosis, portal hypertension or renal disease. Fat-soluble vitamin levels should be monitored and replaced if deficient. Maternal cholestasis may be associated with increased risk of fetal compromise, spontaneous preterm birth and stillbirth.[9] Surrogacy may be an option in the setting of severe maternal phenotype with multi-organ involvement and dysfunction as these would increase probability of poor maternal and perinatal outcomes. The lack of genotype–phenotype correlations has limited the use of genetic data to guide clinical management. International registries would be useful to collate more data to help guide clinical management, inform research priorities and better inform women with ALGS of the maternal and neonatal risks with pregnancy.

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Ethical approval

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Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Guarantor

AM.

Contributorship

AM wrote the first draft of the manuscript. Both authors reviewed and edited the manuscript and approved the final version of the manuscript.

ORCID iD

Adam Morton https://orcid.org/0000-0001-9887-714X

References

1. Hannoush ZC, Puerta H, Bauer MS, et al. New JAG1 Mutation Causing Alagille Syndrome Presenting With Severe Hypercholesterolemia: Case Report With Emphasis on Genetics and Lipid Abnormalities. *J Clin Endocrinol Metab* 2017; 102: 350–353. 2016/12/15.
2. Kamath BM, Baker A, Houwen R, et al. Systematic Review: The Epidemiology, Natural History, and Burden of Alagille Syndrome. *J Pediatr Gastroenterol Nutr* 2018; 67: 148–156. 2018/03/16.
3. Izumi K, Hayashi D, Grochowski CM, et al. Discordant clinical phenotype in monozygotic twins with Alagille syndrome: Possible influence of non-genetic factors. *Am J Med Genet A* 2016; 170A: 471–475. 2015/10/16.
4. Elmslie FV, Vivian AJ, Gardiner H, et al. Alagille syndrome: family studies. *J Med Genet* 1995; 32: 264–268. 1995/04/01.
5. Geenes V and Williamson C. Intrahepatic cholestasis of pregnancy. *World J Gastroenterol* 2009; 15: 2049–2066. 2009/05/07.
6. Geenes VL, Lim YH, Bowman N, et al. A placental phenotype for intrahepatic cholestasis of pregnancy. *Placenta* 2011; 32: 1026–1032. 2011/10/22.
7. Alessandro G, Incerti M and Andreani M. Alagille syndrome: prenatal sonographic findings. *J Clin Ultrasound* 2007; 35: 156–158. 2007/02/14.
8. Wax JR, Chard R, Pinette MG, et al. Two- and three-dimensional prenatal sonographic diagnosis of Alagille syndrome. *J Clin Ultrasound* 2014; 42: 293–296. 2014/01/15.
9. Albayram F, Stone K, Nagey D, et al. Alagille syndrome: prenatal diagnosis and pregnancy outcome. *Fetal Diagn Ther* 2002; 17: 182–184. 2002/03/27.
10. Witt H, Neumann LM, Grollmuss O, et al. Prenatal diagnosis of Alagille syndrome. *J Pediatr Gastroenterol Nutr* 2004; 38: 105–106. 2003/12/17.
11. Jung C, Driancourt C, Baussan C, et al. Prenatal molecular diagnosis of inherited cholestatic diseases. *J Pediatr Gastroenterol Nutr* 2007; 44: 453–458. 2007/04/07.
12. Rahmoune FC, Bruyere M, Tecsy M, et al. Alagille syndrome and pregnancy: anesthetic management for cesarean section. *Int J Obstet Anesth* 2011; 20: 355–358. 2011/09/20.
13. Antsaklis A, Anastasakis E, Mousiolis A, et al. Alagille syndrome. *J Obstet Gynaecol* 2011; 31: 450–451. 2011/06/02.
14. Ferrarese A, Senzolo M and Burra P. Successful pregnancy in Alagille Syndrome. *Dig Liver Dis* 2015; 47: 86–87. 2014/09/28.
15. Maisonneuve E, Morin F, Crochetiere C, et al. Multidisciplinary management of a hepatic and renal transplant patient with Alagille syndrome. *Int J Obstet Anesth* 2012; 21: 382–383. 2012/09/11.
16. Romero R, Reece EA, Riely C, et al. Arteriohepatic dysplasia in pregnancy. *Am J Obstet Gynecol* 1983; 147: 108–109. 1983/09/01.